



# CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA



CAPRISA IS A UNAIDS COLLABORATING CENTRE FOR HIV PREVENTION RESEARCH

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## In this issue...

The lead story for this issue of the newsletter focuses on the announcement that the Fem-PrEP trial is to be closed prematurely due to futility.

The CAPRISA mucosal immunology workshop, which aimed to map out CAPRISA's new mucosal immunology research agenda, is outlined on page 2.

On page 3 we briefly describe the recent visit from the NIH representatives to discuss the Clinical Trial Unit (CTU) recompetition and the visit from the FHI's Protection of Human Subjects Committee.



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## Interim FEM-PrEP trial results provide new insights on HIV prevention

**CAPRISA acknowledges and thanks the FEM-PrEP team for undertaking this critically important high quality study and providing important interim results to guide future HIV prevention research.**

Since tenofovir gel prevents HIV in women and Truvada® tablets prevent HIV in men who have sex with men (MSM), it was hoped that Truvada® tablets will prevent HIV infection in women. The FEM-PrEP trial has established that it is not able to demonstrate a protective effect of Truvada® tablets and one possible interpretation of the study's interim results are that Truvada® may not be as effective in preventing HIV in women compared to its proven effectiveness in preventing HIV infection in MSM.

Professor Salim Abdool Karim, Director of CAPRISA and Pro Vice-Chancellor (Research) at the University of KwaZulu-Natal said that "Science does not always produce the answer we hope for. Thanks to this important trial, we will be able to better understand when, why and how antiretroviral drugs do and do not prevent HIV. I look forward to seeing the complete results and, in particular, an analysis of whether the drug levels in the female genital tract provides any clues to the study's outcome."

The FEM-PrEP trial marks a major point in the field of HIV prevention and its detailed analyses are likely to have to marked influence on future HIV research. CAPRISA wishes the FEM-PrEP team well in the intensive task of closing the study and undertaking the detailed analysis, which are patiently awaited.

FEM-PrEP is a phase III randomized, placebo-controlled, clinical trial designed to assess the safety and effectiveness of a daily oral dose of Truvada® for HIV prevention among women. Truvada® combines two antiretroviral drugs - tenofovir disoproxil fumarate (TDF 300 mg) and emtricitabine (FTC 200 mg) - into a single daily pill, which has been proven safe and effective as a treatment for HIV-infected people. Truvada® prevents HIV from reproducing itself in HIV infected people. The purpose of the FEM-PrEP trial was to test whether daily oral Truvada® could also be used safely and effectively to prevent HIV infection - an approach known as pre-exposure prophylaxis (PrEP).

HIV-negative women between the ages of 18 and 35 who were at higher risk for HIV infection volunteered to take part in FEM-PrEP. The trial was conducted at four sites in three countries: Bondo, Kenya; Bloemfontein and Pretoria, South Africa; and Arusha, Tanzania. Study participants were randomly assigned to receive either Truvada® or a placebo pill. All participants received monthly individual risk-reduction counseling, free condoms, and free treatment for curable sexually transmitted infections. In addition, they had a pregnancy and HIV test monthly.

The main outcomes in the trial are the numbers of HIV infections, side effects and pregnancies in women assigned to Truvada® compared to those assigned to placebo.

Following a scheduled interim review of the FEM-PrEP study data, the Independent Data Monitoring Committee (IDMC) advised that the FEM-PrEP study will be

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## Planning CAPRISA's mucosal immunology research agenda



Attendees of the CAPRISA Mucosal Immunology Workshop included: seated (L-R): Ashley Haase, Laurel Lagenaur, Bruce Walker, Salim Abdool Karim, Quarraisha Abdool Karim, Gustavo Doncel, Marcus Altfeld, and Douglas Kwon. Middle row (L-R): Natasha Samsunder, Tanuja Gengiah, Anneke Grobler, Ayesha Kharsany, Lise Werner, Thumbi Ndung'u, Carolyn Williamson, William Carr, Victoria Kasprovicz, Marianne Mureithi, and Cheryl Baxter. Back row (L-R): Vivek Naranbhai, Nono Mkhize, Lenine Liebenberg, Jo-Ann Passmore, Lindi Roberts, Sengeziwe Sibeko, Anika Naicker, Nelisile Majola, Eugene van der Lingen, and Angela Carr-Hartley

### **A** mucosal immunology workshop was hosted by CAPRISA at the Endless Horizon's hotel in Umhlanga, Durban from 11-13 April 2011.

The purpose of the workshop was to establish a collaborative research agenda within CAPRISA's Tenofovir Research for AIDS Prevention Science (TRAPS) Program. Specifically, available CAPRISA data from the CAPRISA 002 Acute Infection study and CAPRISA 004 tenofovir gel trial were discussed in order to develop synergies across the various disciplines represented at the workshop in order to map out a mucosal immunology research agenda for CAPRISA.

The workshop was attended by several local and international researchers and collaborators from CAPRISA, the University of KwaZulu-Natal, the University of Minnesota Medical School, CONRAD, the University of Cape Town, the National Institutes for Health, the National Institute for Communicable Diseases, and the Ragon Institute of Massachusetts General Hospital, MIT & Harvard University and the HIV Pathogenesis Programme.

The 3-day workshop began with an overview of the CAPRISA 004 tenofovir gel trial results and unanswered questions. A session dedicated to understanding mucosal inflammation and HIV acquisition included presentations by Ashley Haase on "Early mucosal events in HIV infection" and by Gustavo Doncel on "Markers of genital mucosal alteration and risk of HIV infection". These presentations were followed by an overview of genital inflammation in the CAPRISA 004 tenofovir gel trial by Lindi Roberts and Lenine Liebenberg. The afternoon session included presentations by Anita Naicker on localizing HIV infection and tenofovir in mucosal cells in CAPRISA 004

and novel technologies to characterize mucosal immune responses by Douglas Kwon. Nonhlanhla Nono Mkhize presented an overview of neutralizing antibodies in plasma and CVL in the CAPRISA 004 trial. The final session of the day focussed on potential agents for the next generation of combination microbicide gel including an overview of anti-inflammatory agents, glycerol monolaurate (GML) and a lactobacillus microbicide for prevention of inflammation.

The first session on day 2 was dedicated to clinical markers and outcomes. Sengeziwe Sibeko provided data on the clinical disease progression in CAPRISA 004 seroconvertors, while Lise Werner provided data on the relationship between tenofovir levels at seroconversion and its impact on disease progression and Carolyn Williamson shared her data on transmitted virus diversity.

The final session on day 2 was focussed on systemic immune responses. Marcus Altfeld presented on "Early Innate Immune responses: influences on disease progression" while Vivek naranbhai presented on "Systemic inflammation and HIV acquisition in CAP004" and the "Characterisation of the microbiome of the female genital tract". Data on CD4 responses in acute HIV infection in CAPRISA 004 participants was presented by Marianne Mureithi and the final presentation was by Bruce Walker on "What should we expect in T-cell responses following acute infection during tenofovir/ARV use?".

This productive and thought-provoking workshop was concluded with a half day dedicated to discussion and planning on the way forward for the mucosal immunology research agenda at CAPRISA.



## Fem-PrEP trial results

*Continued from page 1.....*

highly unlikely to be able to demonstrate Truvada®'s effectiveness in preventing HIV infection in the FEM-PrEP study population even if it continued to its originally planned conclusion. FHI therefore decided to initiate an orderly closure of the study over the next few months. The final analyses have not yet been conducted. At this time, it cannot be determined whether or not Truvada® works to prevent HIV infection in women.

Only preliminary FEM-PrEP data as of 18 February 2011 are available at this time:

- About 90 % of the participants were retained in the study.
- Adherence to study product was approximately 95 % when the study product was available for use
- The HIV incidence rate was 5% per year
- 28 of the 56 HIV infections occurred in women assigned to Truvada® and 28 occurred in women assigned to a placebo pill.
- The overall pregnancy rate was 9%.
- Pregnancy rates were higher in women in the Truvada® arm compared to women assigned to the placebo arm. This was unexpected and inconsistent with known drug interactions involving tenofovir (TDF) and contraceptive hormones, and with known metabolic effects of emtricitabine (FTC). Possible explanations include differential pill adherence by group, previously undefined drug-drug interactions, chance, or a combination of factors (including yet unknown factors).
- The use of Truvada® was associated with some known side effects that were not serious.

Further analyses of the data are not expected until several months from now.

**For more information regarding the FEM-PrEP clinical trial please contact Beth Robinson, associate Director, Project Communications E-mail: [brobinson@fhi.org](mailto:brobinson@fhi.org)**

## Discussing the Clinical Trial Unit recompetition with NIH



*Seated (L-R): Edward Handelsman, Mary Kirker and Manizhe Payton, standing (L-R): Thola Bennie, Marian Swart, Cheryl Baxter, Nesri Padayatchi, Sunita Panday, Quarraisha Abdool Karim, Janet Frohlich, Devenie Latchman, Nasrin Amla, Daya Moodley, Day Munatsi, Kogieleum Naidoo, Ayesha Kharsany and Tanuja Gengiah*

Representatives from the NIH, including: Manizhe Payton, Director of the Office of Clinical Site Oversight, Mary Kirker, Branch Chief of Grants Management, and Edward Handelsman, Chief of the International Maternal Adolescent Pediatric Branch Therapeutics Research Program visited and met with key CAPRISA staff on March 23, 2011 to discuss the upcoming NIH Clinical Trial Unit (CTU) recompetition. Topics covered included size and scope of CTUs, role of international sites and funding. Other scientific issues discussed included: network scientific agendas, integration and retention of junior Investigators, and incorporation of scientific ideas from Non-Network Investigators. While in South Africa, the NIH team also visited with other South African researchers in Durban, Johannesburg and Cape Town who are currently participating in Network-related studies funded by the NIH.

## Representatives from FHI's PHSC visit CAPRISA



*Seated (L-R): Steve Shaber and Sara Tenorio, standing (L-R): Doug Wasenaar, Marian Swart, Susan Dull, and Salim Abdool Karim*

The chair of FHI's Protection of Human Subjects Committee (PHSC), Steve Shaber, accompanied by the PHSC Manager, Sara Tenorio, and a member of FHI's Board of Directors, Susan Dull, visited CAPRISA on the 7 April 2011 and met with key staff from the CAPRISA 004 study team members and toured the eThekweni site. During their time at CAPRISA they had an opportunity to observe screening, enrollment and the informed consent of a participant enrolling into ongoing trials. In addition to visiting the CAPRISA site, the purpose of their trip to Africa between 4-15 April was also to visit a few of the FEM-PrEP sites during their trip, including the Setshaba site in Pretoria and the Bondo, Kenya site.

## 2011 Scientific publications



- 1 **Gengiah TN, Gray AL, Naidoo K, Abdool Karim Q.** Initiating antiretrovirals during tuberculosis treatment: a drug safety review. *Expert Opin. Drug Saf.* 2011 doi: 10.1517/14740338.2011.546783
- 2 **Singh JA.** The challenge of discharging research ethics duties in resource-constrained settings. *PLoS Medicine* 2011 8(3): e1000421
- 3 Gezmu M, DeGruttola V, Dixon D, Essex M, Halloran E, Hogan J, **Grobler A**, Kim S, McDermott J, McKaiga R, Neaton JD. Strengthening biostatistics resources in sub-Saharan Africa: Research collaborations through U.S. Partnerships. *Statistics in Medicine.* 2011, DOI: 10.1002/sim.4144
- 4 Moodley J, Pattinson R, **Baxter C, Sibeko S, Abdool Karim Q.** Strengthening HIV services for pregnant women: an opportunity to reduce maternal mortality rates in Southern Africa/sub-Saharan Africa. *BJOG* 2011;118:219–225.
- 5 Singh R, Gaiha G, **Werner L**, McKim K, **Mlisana K**, Luban J, Walker BD, **Abdool Karim SS**, Brass AL, Ndung'u T. Association of TRIM22 with the type 1 interferon response and viral control during primary HIV-1 infection *Journal of Virology* 2011, 85(1): 208-216
- 6 Moore, PL Gray ES, Sheward D, Madiga M, Ranchobe N, Lai Z, Honnen WJ, Nonyane M, Tumba N, Hermanus T, **Sibeko S, Mlisana K, Abdool Karim SS, Williamson C**, Pinter A, **Morris L**, and the CAPRISA 002 study. Potent and broad neutralization of HIV-1 subtype C 1 viruses by plasma 2 antibodies targeting a quaternary epitope including residues in the V2 loop. *J Virol* 2011, 85(7): 3128-3141
- 7 Heidari S, Eckert MJ, Kippax S, **Abdool Karim Q**, Sow PS, Wainberg MA. Time for gender mainstreaming in editorial policies. *Journal of the International AIDS Society* 2011, 14:11doi:10.1186/1758-2652-14-11
- 8 **Abdool Karim Q, Kharsany ABM, Frohlich JA, Baxter C, Yende N, Mansoor LE, Mlisana KP, Maarschalk S, Arulappan N, Grobler A, Sibeko S, Omar Z, Gengiah TN, Mlotshwa M, Samsunder N, Abdool Karim SS.** Recruitment of high risk women for HIV prevention trials: baseline HIV prevalence and sexual behavior in the CAPRISA 004 tenofovir gel trial. *Trials* 2011, 12:67
- 9 Gray ES, Madiga MC, Hermanus T, Moore PL, Wibmer CK, Tumba NL, **Werner L, Mlisana K, Sibeko S, Williamson C, Abdool Karim SS, Morris L** and the CAPRISA 002 Study Team. The Neutralization Breadth of HIV-1 Develops Incrementally over Four Years and Is Associated with CD4 T Cell Decline and High Viral Load during Acute Infection. *J Virol* 2011, doi:10.1128/JVI.00198-11
- 10 **Abdool Karim SS**, Richardson BA, Ramjee G, Hoffman IF, Chirenje ZM, Taha T, Kapina M, Maslankowski L, Coletti A, Profy A, Moench TR, Piwowar-Manning E, Mâsse B, Hillier SL, Soto-Torres L on behalf of the HPTN 035 Study Team. Safety and Effectiveness of BufferGel and 0.5% PRO2000 Gel for the Prevention of HIV Infection in high-risk Women. *AIDS* 2011, 25(7):957-966.
- 11 **Abdool Karim Q, Kharsany ABM, Naidoo K, Yende N, Gengiah T, Omar Z, Arulappan N, Mlisana KP, Abdool Karim SS.** Co-enrollment in multiple HIV prevention trials — Experiences from the CAPRISA 004 Tenofovir gel trial. *Contemporary Clinical Trials* 2011, doi:10.1016/j.cct.2011.01.005
- 12 **Ramsuran V**, Kulkarni H; He W; **Mlisana K**, Wright E, **Werner L**, Castiblanco-Quinche J, Dhanda R, Le T, Dolan M, Guan W, Weiss R, Clark R, **Abdool Karim S**, Ahuja SK, Ndung'u T. Duffy-Null-Associated Low Neutrophil Counts Influence HIV-1 Susceptibility in High-Risk South African Black Women. *Clinical Infectious Diseases* 2011;52(10):1248–1256

## Upcoming Conference & Workshop Reminders

| Conference   | dates            | Deadlines             |                  |   |
|--|------------------|-----------------------|------------------|---|
|  |                  | Abstracts             | Registration     | website   |
| 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention | 17-20 July, 2011 | 23 May (late breaker) | 24 February 2011 | <a href="http://www.ias2011.org/">www.ias2011.org/</a>        |
| 4th SA AIDS Conference   | 7-10 June 2011   | 28 January 2011       | 20 May 2011      | <a href="http://www.sa aids.com/">http://www.sa aids.com/</a> |

CAPRISA is an official research institute of the University of KwaZulu-Natal.  
 CAPRISA was established in 2002 through a CIPRA grant from the NIH, as a multi-institutional collaboration, incorporated as an independent non-profit AIDS Research Organization

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